Remarks/Arguments

The foregoing amendments include the cancellation of non-elected claims 12-20, and amendments of formal nature in the specification and the remaining claims. The amendments do not add new matter.

Election/Restrictions

Applicants note the rejoinder of claims 27-31 with the original Group I claims (1-11 and 21-26). Accordingly, and also in view of the present amendment, claims 1-11 and 21-31 are pending and under examination in the present application. All claims stand rejected on various grounds, which will be addressed hereinbelow.

Drawings

According to the Notice of Draftsperson's Patent Drawing Review, Figures 1-5 were rejected since the top margins were unacceptable. New drawings, which are believed to comply with all formal requirements, are submitted with the present Amendment and Response.

Specification

The disclosure has been objected to for containing an embedded hyperlink and/or other form of browser-executable code on page 6, line 10. The foregoing amendment to the specification is believed to overcome this objection.

Claim Objections

Claims 21 and 27 were objected to under 37 C.F.R. 1.75 "as being a substantial duplicate of one another."

Applicants respectfully disagree. Claim 21 recites a host cell that is transformed with an *expression vector* comprising a nucleic acid *encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3*. Claim 27 is directed to a cell comprising an *exogenously supplied nucleic acid*, that *encodes SEQ ID NO: 1 or SEQ ID NO: 3*. Accordingly, claim 1 requires the presence of an expression vector, and encompasses cells that are transformed with an expression vector that carries a nucleic acid encoding a polypeptide including, but not limited to, the sequence of SEQ ID NO: 1 or 3. In contrast, the language of claim 27 does not

require the presence of an expression vector. Indeed, it is well known in the art that naked DNA can be incorporated into a cell without the use of vectors, e.g. by electroporation or protoplast fusion. Furthermore, claim 27 is directed to cells that comprise nucleic acid encoding SEQ ID NO: 1 or 3 (and not polypeptides comprising such sequences).

Accordingly, while the two claims have overlapping scopes, the differences go well beyond "a slight difference in wording." Since the two claims are that "a substantial duplicate of one another," the Examiner is respectfully requested to reconsider and withdraw this objection.

Claims Rejections - 35 U.S.C. § 112

1. Claims 21-31 were rejected under 35 U.S.C. § 112, first paragraph for alleged lack of support in the specification for the term "progeny thereof" recited in claims 21 and 27-30. Since the term objected to is no longer present in the claims, the present rejection is believed to be moot.

2. Claims 1-11 were rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Although this language appears to indicate that the claims are rejected for alleged lack of enablement, the rest of the rejection argues lack of written description. Accordingly, the rejection will be addressed as a written description rejection.

According to the rejection, the "written description of this instant case only sets forth nucleic acids, SEQ ID NO: 2 and 4, which encode polypeptides, SEQ ID NO: 1 (Edg4) and 3 (Edg5), respectively." The Examiner finds that this written description "is not commensurate in scope with claims drawn to polynucleotides encoding variant and mutated polypeptides embodied by the listed claims."

Applicants disagree, and submit that the specification of the present application as filed clearly allows persons of ordinary skill in the art to recognize that applicants were in the possession of the invention as currently claimed.

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. § 112, first paragraph is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." In re

Kaslow, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). In Enzo Biochem, Inc. v. Gen-Probe Inc, 285 F.3d 1013, 62 U.S.P.Q.2d 1289 (Fed. Cir. 2002), the Federal Circuit additionally noted that the showing of "possession" is secondary to the statutory mandate that the specification shall contain a written description of the invention, and that requirement is not met if, despite a showing of possession, the specification does not adequately describe the claimed invention. The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See, e.g. Vas-Cath, 935 F.2d at 1563; 19 USPQ2d at 1116. The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Union Oil v. Atlantic Richfield Co., 208 F.3d 989, 996 (Fed. Cir. 2000).

In Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), the Federal Circuit held that an adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties." A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequences, falling within the scope of the genus or a recitation of structural features to the members of the genus, which features constitute a substantial portion of the genus. *Id.* 119 F.3d at 1569, 43 USPQ2d at 1406. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, 'Written Description' Requirement, 66 F.R. 1099, 1106 (January 5, 2001) (hereinafter "Written Description Guidelines") provide that applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Written Description Guidelines at 1106.

Accordingly, whether a specification shows that Appellants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including level of knowledge and skill in the art, partial structure, physical and/or chemical properties, functional characteristics along or coupled with a known or disclosed correlation between structure and function, etc. The inventor is not required to

describe every single detail of his invention. An applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention is from the field of recombinant DNA technology. It is well established that the level of skill in this field is relatively high, and is represented by a Ph.D. scientist having several years of experience in the pertinent field.

The present application specifically discloses two polypeptide species the coding sequences of which are encompassed by the claims. The broadest claims currently pending allow 5% variation from the polypeptide sequences actually disclosed. The two disclosed species, Edg4 and Edg5, are members of the family of Edg polypeptides, and show significant degree of homology with other members of that family. Indeed, Edg4 was found to be 72% similar to the human Edg2 LPA receptor. The specification additionally discloses structural features within the Edg4 sequence, including boundaries of the seven transmembrane regions, glycosylation sites, phosphorylation sites, and conserved regions/differences compared to other seven-transmembrane receptors (page 42, lines 10-24). Similarly, Edg5 is identified as a member of the Edg family of receptors, with significant sequence homology to other members. In addition, Edg5 is found to be the human ortholog of rat S1P receptor H218/AGR16. (Page 47, lines 5-11.) In addition, the specification (pages 9-13) teaches modifications within the native Edg4 and Edg5 sequences specifically disclosed.

It is submitted that in view of the disclosure in the specification, and also in view of general knowledge available in the art at the relevant time about other members of the Edg family of receptors, a person skilled in the art would have recognized that applicants were in the possession of the invention as claimed at the effective filing date of the present application. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

3. Claim 24 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly filing to provide adequate written description for the Tsup-1 human T lymphoblastoma cell line. This cell has been deposited with the ATCC under the designation SUP-T1[VB] and accorded the accession number CRL-1942. Since samples of the Tsup-1 (SUP-T1) cell line are freely available from ATCC, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

4. Claims 1, 3, and 6-11 were rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement commensurate with the scope of the claimed invention. Although the Examiner acknowledges that the specification teaches modifications within the native Edg4/5 sequences, she maintains that there is no evidence which modifications yield polypeptides that maintain the activities proposed in the specification.

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also* Amgen Inc. v. Chugai Pharms. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991).

"Enablement is not precluded by the necessity for some experimentation ... [the] experimentation needed to practice the invention must not be undue experimentation." Enzo Biochem, Inc. v. Calgene, Inc. 188 F.3d 1362, 1371 (Fed. Cir. 1999). Further, "the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (C.C.P.A. 1970). "While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1366, 42 USPQ2d 1001 (Fed. Cir. 1997)

"In both *ex parte* and *inter partes* contexts, an enablement determination is made *retrospectively*, *i.e.*, by looking back to the filing date of the patent application and determining whether undue experimentation *would have been* required to make and use the claimed invention at the time..." Enzo at 1372. (emphasis in the original). In In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988), the Federal Circuit set forth a number of factors that may be considered in making a determination as to whether a disclosure would require undue experimentation to enable an invention. The factors, which may be reviewed include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The *Wands* factors are illustrative, not mandatory and "[w]hat is relevant depends on the facts." Enzo, at 1371.

As stated in In re Armbruster, 512 F.2d 676, 677-78, 185 USPQ 152, 153 (CCPA 1975), quoting from In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 369-70 (CCPA 1971):

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis [lack of enablement] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

It is believed that the Examiner failed to establish a *prima facie* case of lack of enablement. Based on examples from the general field of protein chemistry, the Examiner concludes that "it is clear that the predictability of changes to the amino acid sequence is practically nil as far as biological activities are concerned." This is, of course, not generally true. As discussed above, the present Edg4/5 proteins have been identified as members of the family of Edg receptors, and the specification includes several structural characteristics within their sequences. Accordingly, one skilled in the art would know which changes within the molecule are least likely to result in a loss of biological activity. While identification of the residues to be altered within the confines of 5% difference relative to the specific sequences disclosed might require some experimentation, such experimentation would not be "undue" and would, therefore, not preclude enablement within the full scope of claims currently pending. Accordingly, the Examiner is respectfully requested to withdraw the present rejection.

5. Claims 3-5 were rejected under 35 U.S.C. § 112, second paragraph as "being indefinite" in their recitation of the phrases "sequence selected" and "hybridize under high stringency conditions." Since the claims no longer contain the language objected to, the present rejection is believed to be moot.

Claim Rejections - 35 U.S.C. § 101

Claims 1-11 were rejected since "the claimed invention is not supported by either a specific, credible or substantial asserted utility or a well established utility."

Since the rejection does not encompass the claims reciting the specific Edg4/5 sequences disclosed in the specification, it is related to the scope of the more generic claims. Citing examples of the unpredictability of functional characteristics based on structural similarity, the

Examiner concludes that applicants failed to provide patentable utility within the full scope of the genus claims in claims 1-11.

Applicants have established a substantial, specific and credible utility for the Edg4 and Edg5 proteins of SEQ ID NOS: 1 and 3, respectively. However, it is well known in the art that variants of native proteins, such as C-terminally truncated, or transmembrane-domain deleted variants, can be typically used for the same purposes as the native full-length sequences of the respective polypeptides. Thus, it was clear for those skilled in the art at the filing date of the present application that the native proteins of SEQ ID NO: 1 and SEQ ID NO: 3 of the present application can be altered, without losing their biological activity. As discussed above in connection with the "lack of enablement" and "lack of adequate written description" rejections, the present Edg4/5 proteins have been identified as members of the family of Edg receptors, and the specification includes several structural characteristics within their sequences. Accordingly, one skilled in the art would know which changes within the molecule are least likely to result in a loss of biological activity. Accordingly, the withdrawal of the present rejection is respectfully requested.

Claim Rejections - 35 U.S.C. § 102

1. Claims 1-11 were rejected under 35 U.S.C. § 102(e) "as being anticipated" by U.S. Patent No. 6,020,158 (the '158 patent, filed May 22, 1997). According to the rejection, this document discloses nucleic acid encoding an Edg4 protein that is at least about 75% identical to the amino acid sequence of SEQ ID NO: 1, is at least about 75% identical to SEQ ID NO: 2 of the present application, and will hybridize under high stringency conditions to the nucleic acid complement of a sequence of SEQ ID NO: 2.

The '158 patent discloses a 351 amino acids long polypeptide sequence that contains the following mutations relative to amino acids 1-351 of the Edg4 amino acid sequence of SEQ ID NO: 1: Phe213Leu; Ser300Ala; Ser318Pro; and Thr,Pro,ProPhe(348-351)Asp,Ser,Thr,Leu, and lacks the rest of the C-terminus of the 382 amino acids long Egd-4 sequence (SEQ ID NO: 1) of the present invention. Accordingly, while the sequence identity for the 1-351 amino acids region is over 99%, the sequence identity is only about 91%, when sequence identity is calculated relative to the full-length of SEQ ID NO: 1.

Since the invention as currently claimed is clearly distinguished over the '158 patent, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

2. Claims 1, 3, and 5-11 were rejected under 35 .S.C. 102(e) "as being anticipated" by U.S. Patent No. 5,856,443 (the '443 patent, filed December 6, 1996). According to the rejection, the '443 patent discloses sequence 1, an isolated nucleic acid encoding the Edg5 protein (SEQ ID NO: 3), which encodes the protein set forth as sequence 2, which is at least 85% identical to the amino acid sequence of SEQ ID NO: 3.

The '443 patent discloses an amino acid sequence, which is about 87.8% identical with the Edg5 amino acid sequence of the present invention (SEQ ID NO: 3). Since the current claims are clearly distinguished over this sequence, the Examiner is respectfully requested to reconsider with withdraw the present rejection.

3. Claims 1, 3, and 5-9 were rejected under 35 U.S.C. § 102(b) "as being anticipated" by GenBank Accession number AA419064, clone 755526 (May 12, 1997).

Claim 5 has been canceled. The rejection of claims 1, 3, and 6-9 is respectfully traversed. AA419064 is a 353 nucleotide long EST sequence, which corresponds to nucleotides 14-392 of the 1734 nucleotides long SEQ ID NO: 2 of the present application. As discussed on page 42 of the present application, this EST sequence has significant, but not identical, homology to the 5' region of the Edg2 cDNA clone, and was use to obtain the Edg4 clone (SEQ ID NO: 2) of the present application. However, before the present invention, there has been no indication in the art that this EST sequence would have encoded any polypeptide, or would have been part of a longer sequence encoding a polypeptide. Accordingly, the cited EST sequence does not anticipate claims 1, 3, or 6-9, and the withdrawal of the present rejection is respectfully requested.

4. Claims 1-5 were rejected under 35 U.S.C. § 102(b), "as being anticipated" by MacLennan *et al., Molecular and Cellular Neurosciences* 5:201-206 (1994).

MacLennan *et al.* appears to be the scientific counterpart of U.S. Patent No. 5,856,443 (the '443 patent) discussed above. Just as the '443 patent, the cited paper discloses an amino acid sequence, which is about 87.8% identical with the Edg5 amino acid sequence of the present

invention (SEQ ID NO: 3). Since the current claims are clearly distinguished over this sequence, the Examiner is respectfully requested to reconsider with withdraw the present rejection.

5. Claims 1-3 and 5-11 were rejected under 35 U.S.C. § 102(a) as "being anticipated" by An *et al.*, *J. Biol. Chem.* 273:7906-7910 (April 3, 1998), which, according to the rejection, "discloses an Edg4 protein that is at least about 85% identical to SEQ ID NO: 1."

An *et al.* discloses an amino acid sequence (GenBank Accession No. AF011466) that is identical with the Edg4 polypeptide sequence (SEQ ID NO: 1) of the present application. It is well established that applicants' disclosure of their own work within the year before the filing date of a patent application cannot be used against applicants under 35 U.S.C. 102(a). In re Katz, 687 F.2d 450, 215 USPQ 14 (1982). In the present case, the inventors of the present application (Edward J. Goetzel and Songzhu An) are co-authors of the cited publication. Enclosed is a Declaration signed by Drs. Goetzel and An establishing that the cited article describes their own work to which the other two co-authors made no inventive contribution. This Declaration is believed to remove An *et al.* as a reference. Accordingly, the withdrawal of the present rejection would be in order.

Applicants are pleased to note that claims 21-31 were found to be free of prior art. It is believed that upon entry of the present amendment and consideration of the current arguments, all claims will be found allowable. An early issuance of a Notice of Allowance is respectfully solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims. The attached sheet is captioned "**Version with markings to show changes made.**"

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: November 6, 2002

By: _____

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Version with markings to show changes made

In the Specification:

The paragraph starting at page 6, line 3 has been amended as follows:

-- As used herein, the term "percent (%) amino acid sequence identity" means the value obtained using the BLASTP program of the BLAST 2.0 program family (using default parameters) described by Altschul *et al.*, Nucleic Acids Res. (1997) 25:3389-3402[, and accessible through the World Wide Web (WWW) at http://www.ncbi.hin.gov/BLAST]. --

In the Claims:

Claims 2 and 5 have been canceled.

Claims 1, 3, 4, 21, and 27-30 have been amended as follows:

1. (Once Amended) An isolated nucleic acid encoding an Edg protein comprising an amino acid sequence having [that is] at least [about 85% identical] 95% sequence identity to the full length of the amino acid sequence [selected from the group consisting] of [SEQ ID NOS: 1, 3] SEQ ID NO: 1 or SEQ ID NO: 3.

3. (Once Amended) An isolated nucleic acid according to claim 1 encoding the amino acid sequence [selected] of SEQ ID NO: 1 or SEQ ID NO: 3.

4. (Once Amended) An isolated nucleic acid according to claim [2] 1 comprising the nucleic acid sequence [selected] of SEQ ID NO: 2 or SEQ ID NO: 4.

21. (Once amended) A host cell transformed with an expression vector comprising a nucleic acid encoding a polypeptide comprising the amino acid sequence [selected from the group consisting] of SEQ ID NO: 1 [and] or SEQ ID NO: 3.

27. (Once amended) A cell comprising an exogenously supplied nucleic acid which comprises a polynucleotide sequence that encodes a polypeptide of SEQ ID NO: 1 [and] or SEQ ID NO: 3[, or progeny thereof].

28. (Once amended) The cell of claim 27 in which the polynucleotide is selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 4[, or progeny thereof].

29. (Once amended) The cell of claim 27 or 28 which is selected from the group consisting of a Jurkat leukemic T cell and a Tsup-1 human T lymphoblastoma cell[, or progeny thereof].

30. (Once amended) The cell of claim 27 or 28 which further comprises an exogenously supplied reporter nucleic acid[, or progeny thereof].

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